(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2002 (24.01.2002)

PCT

(10) International Publication Number
WO 02/05820 A1

(51) International Patent Classification[7]: A61K 31/495, 31/505

(21) International Application Number: PCT/US01/22538

(22) International Filing Date: 18 July 2001 (18.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/619,899 19 July 2000 (19.07.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/05820 A1

(54) Title: SILDENAFIL CITRATE SOLID DISPERSIONS HAVING HIGH WATER SOLUBILITY

(57) Abstract: Solid dispersions of sildenafil citrate and certain highly water soluble sugars are provided, which solid dispersions significantly increase the water solubility of sildenafil citrate. Methods for preparing highly water soluble solid dispersions of the present invention facilitate the incorporation of sildenafil citrate into new sildenafil citrate containing dosage forms which were heretofore impractical. A method for improving and/or enhancing the sexual response in animals, particularly humans, by administering such new sildenafil citrate containing dosage forms is also provided.

SILDENAFIL CITRATE SOLID DISPERSIONS HAVING HIGH WATER SOLUBILITY

This Application is a continuation-in-part of U.S. Patent Application Serial No. 09/434,878, filed November 5, 1999; and International Patent Application Number PCT US99/31327, filed December 30, 1999; both of which claim priority to U.S. Provisional Application Serial No. 60/116,823, filed January 21, 1999; the disclosures of each of which are incorporated herein by reference as if set forth herein in their entireties.

The present invention is directed to improving and/or enhancing the sexual response in animals, particularly humans, by administering the compositions and dosage forms described herein. Specifically, the present invention relates to dosage forms containing sildenafil citrate/highly water soluble sugar solid dispersions having high water solubility. The present invention also relates to methods for making sildenafil citrate/highly water soluble sugar solid dispersions and dosage forms or drug delivery systems incorporating such solid dispersions.

Sildenafil citrate is a pharmocologic agent which has proven useful in the treatment of certain forms of sexual dysfunction. Specifically, sildenafil citrate is widely used in the treatment of erectile dysfunction in men. That is, in the United States alone, it is estimated that more than 5,000,000 men have used sildenafil citrate (i.e. Viagra®) to treat erectile dysfunction.

Sildenafil exhibits an absolute bioavailability of about 40% and is reported to result in maximum observed plasma concentrations within 30 to 120 minutes following oral dosing in a fasted state. The rate of absorption is reduced if taken with a high fat meal.

Sildenafil citrate exhibits a low water solubility, namely about 3.5 mg/mL. This low water solubility of sildenafil citrate coupled with its high presystemic elimination have contributed to its low oral bioavailability. Several factors may affect a therapeutic agents bioavailability including the dosage form used and various properties of the agent, e.g., the dissolution rate of the agent. Poor bioavailability is a significant problem encountered in the development of many pharmaceutical compositions, particularly those containing an active ingredient that is poorly water soluble. "Poorly water soluble therapeutic agents", i.e., those

having a water solubility of less than about 10 mg/mL, tend to be eliminated from the gastrointestinal tract before being completely absorbed into the circulatory system. The bioavailability of many poorly water-soluble drugs is limited by the dissolution rates of those drugs. Often non-oral administration routes, for example, through sublingual, rectal and vaginal mucosae, have been used to avoid the presystemic elimination encountered with oral administration routes. These non-oral administration routes, however, offer limited biological fluid to dissolve drugs rapidly for absorption. Therefore, such non-oral administration routes are limited for use with drugs having relatively high water solubility and high membrane permeability.

Accordingly, what is needed is a technique for increasing the water solubility and membrane permeability of sildenafil citrate to provide for increased bioavailability of sildenafil citrate and to facilitate the incorporation of sildenafil citrate into various, heretofore impractical, dosage forms.

Glossary

The following definitions are provided to facilitate understanding of certain terms used frequently herein.

The term "bioavailability" as used herein and in the appended claims is the percentage of dose that reaches the systemic circulation intact, when not directly injected into the circulation. Bioavailability is clinically important because pharmacological and toxic effects are proportional to both dose and bioavailability. When bioavailability is low, inter- and intra-subject variability in bioavailability are magnified and incomplete bioavailability can become a serious concern. Moreover, cost effectiveness can be increased by maximizing the bioavailability of a drug.

The term "coating solution" as used herein and in the appended claims is a viscous and homogenous mixture of hydrocolloids, sildenafil citrate/highly water soluble sugar solid dispersion and other additives in a solvent. The coating solution is treated according to the method of the present invention to form a mucosal surface-coat-forming film dosage form.

The term "disintegration time" as used herein and in the appended claims is the time in seconds at which a mucosal surface-coat-forming film dosage form of the present

invention breaks when brought into contact with water or saliva. In a preferred embodiment of the present invention, the disintegration time ranges from 1 to 300 seconds.

The term "dissolving time" as used herein and in the appended claims is the time in seconds or minutes at which not less than 80% of the tested mucosal surface-coat-forming film dosage form of the present invention is dissolved in an aqueous media or saliva. In a preferred embodiment of the present invention, the dissolution time ranges from 10 to 600 seconds.

The term "dry tack" as used herein and in the appended claims is a quantitative value for tackiness (grams) of dry film by Texture Analyzers (Model TA.XT2i with 6mm diameter stainless steel cylinder probe) from Texture Technologies Corp. The tackiness after the addition of 10 μL of water on the same surface area is defined as the "wet tack" (gram) to simulate the adhesion of the mucosal surface-coat-forming film dosage form of the present invention upon contact with a moist mucosal surface. In a preferred embodiment of the present invention, the dry tack ranges from 0.2 to 3.5 grams, with a preferred range of 0.4 to 2.0 grams and the wet tack is in the range of 35 to 150 grams with a preferred range of 40 to 100 grams.

The term "% elongation" as used herein and in the appended claims is measured when a mucosal surface-coat-forming film dosage form of the present invention snaps as sufficient force is applied to exceed the elastic limit thereof.

The term "hydration rate" as used herein and in the appended claims is the speed of absorbing water at 25°C and 75% relative humidity in 24 hours.

The term "modulus" as used herein and in the appended claims is a measurement of the stiffness of a mucosal surface-coat-forming film dosage form of the present invention.

The term "mucosal surface-coat-forming" as applied to a film as used in this description and in the appended claims, unless specified otherwise herein, means a film that coats the mucosal surface on contact, and may not thereafter be manually recovered or moved from the contact site; and subsequently disintegrates and dissolves so as to release the sildenafil. It should be noted that for purposes of the description of the present invention and the following claims, "mucosal surface" means any moist surface of the body, including the

surfaces in the human body identified in **Figure 1** and in the oral cavity identified in **Figure 2.**

The term "percentage of swelling" as used herein and in the appended claims is the percentage of the initial volume that is increased before dissolving. In a preferred embodiment of the invention, the percentage of swelling is less than 10% in 60 seconds.

The term "permeation enhancer" as used herein and in the appended claims is a natural or synthetic molecule which facilitates the absorption of the sildenafil through a mucosal surface.

The term "release study" as used herein and in the appended claims is the percentage of sildenafil citrate released from a mucosal surface-coat-forming film dosage unit of the present invention as a function of the time in a suitable dissolution vessel and medium under specified conditions of temperature and pH.

The term "sexual dysfunction" as used herein and in the appended claims generally includes any sexual dysfunction in an animal, preferably a mammal, more preferably a human. The animal can be male or female. Sexual dysfunction may include, for example, sexual desire disorders, sexual arousal disorders, orgasmic disorders and sexual pain disorders. Female sexual dysfunction refers to any female sexual dysfunction including, for example, sexual desire disorders, sexual arousal dysfunction, orgasmic dysfunction, sexual pain disorders, dyspareunia, and vaginismus. The female can be pre-menopausal or menopausal. Male sexual dysfunction refers to any male sexual dysfunction including, for example, male erectile dysfunction and impotence.

The term "sildenafil citrate/highly water soluble sugar solid dispersion" as used herein and in the appended claims means a solid dispersion of sildenafil citrate and a highly water soluble sugar.

The term "sildenafil citrate/xylitol sold dispersion" as used herein and in the appended claims means a solid dispersion of sildenafil citrate and xylitol.

The term "solid dispersion" as used herein and in the appended claims is a dispersion of sildenafil citrate in an inert carrier or matrix, namely a highly water soluble sugar, at solid state. The concept of solid dispersions was discussed by Sekiguchi and Obi in 1961 (Chem. Pharm. Bull. 9, 866).

The term "subject" as used herein and in the appended claims is an animal, preferably a mammal, more preferably a human, most preferably a human male.

The term "tear propagation resistance" as used herein and in the appended claims is the average force in Newton's (N) necessary to propagate a tear across a mucosal surface-coat-forming film dosage form of the present invention under a specified rate of extension as defined in ASTM D1938 and is interpreted from the load time chart. In a preferred embodiment of the present invention, the tear resistance ranges from 0.001 to 1 N with a preferred range of 0.01 to 1 N.

The term "tensile strength" as used herein and in the appended claims is expressed in pounds per square inch (psi) and is the property of the mucosal surface-coat-forming film dosage form of the present invention that requires a load to cause load deformation failure of said film.

The term "thickness" as used herein and in the appended claims by measurements in mil (a mil=one thousandth of an inch) is determined when a mucosal surface-coat-forming film dosage form of the present invention is placed between two microscopic slides.

The term "water content" as used herein and in the appended claims is the % residual water content per unit dose as measured to the Karl Fisher method and expressed as percent of the dry weight of the mucosal surface-coat-forming film dosage form of the present invention.

Summary of the Invention

It has been found surprisingly that the incorporation of sildenafil citrate into a solid dispersion with certain highly water soluble sugars results in a marked increase in the water solubility of the sildenafil citrate. This resultant increase in the water solubility of sildenafil citrate will facilitate the incorporation of sildenafil citrate into various, heretofore impractical, dosage forms.

The present invention provides compositions and dosage forms comprising sildenafil citrate, wherein the water solubility of sildenafil citrate is significantly increased. This increase in water solubility (1) provides for an increased oral bioavailability of the sildenafil

citrate, and (2) accommodates the incorporation of sildenafil citrate into dosage forms or delivery systems such as nasal sprays or aerosols, mucoadhesive devices for sublingual, vaginal and/or rectal administrations. Such delivery systems by-pass first-pass metabolism and provide for rapid onset of therapeutic action, both of which are highly preferred for this class of medication. Moreover, the present invention facilitates a reduction in the required size of the sildenafil citrate unit dose. This reduction in the sildenafil citrate unit dose can reduce the occurrence and severity of adverse side effects and reduce the cost of manufacturing of the dosage forms or delivery systems containing sildenafil citrate.

In a preferred embodiment of the present invention, dosage forms are provided which include sildenafil citrate and a highly water soluble sugar. Preferably, the sildenafil citrate and the highly water soluble sugar used in the dosage forms of the present invention form a solid dispersion. Preferably, the solid dispersion will be 5 to 95% highly water soluble sugar by weight, more preferably 5 to 75%, most preferably 10 to 50%.

Preferably, the sildenafil citrate/highly water soluble sugar solid dispersions used in the dosage forms of the present invention will have a water solubility of at least 20 mg/mL, more preferably at least 30 mg/mL, yet more preferably at least 40 mg/mL, most preferably at least 50 mg/mL. Preferably, the highly water soluble sugar used to form the sildenafil citrate/highly water soluble sugar solid dispersion will be a highly water soluble sugar, such as, for example, mannitol, xylitol, sorbitol, sucrose, dextrose, galactose, lactose, fructose and maltose. More preferably, the highly water soluble sugar used to form the sildenafil citrate/highly water soluble sugar solid dispersion will be selected from the group consisting of mannitol, xylitol and sorbitol. Most preferably, the highly water soluble sugar used to form the sildenafil citrate/highly water soluble sugar solid dispersion will be xylitol.

In a preferred aspect, the present invention provides dosage forms including a sildenafil citrate/highly water soluble sugar, wherein the highly water soluble sugar is mannitol, xylitol, sorbitol or a mixture thereof, most preferably, the highly water soluble sugar is xylitol. Preferably, the mass ratio of sildenafil citrate to highly water soluble sugar in these solid dispersions will be 19:1 to 1:19, more preferably 9:1 to 1:3, still more preferably 9:1 to 1:1, most preferably 9:1.

In another preferred aspect, the present invention will enable the effective use of sildenafil citrate in a variety of heretofore impractical dosage forms. Preferably, the present

invention will enable the use of sildenafil citrate in, for example, mucoadhesive nasal sprays, effervescent tablets, mucoadhesive sublingual discs, mucosal surface-coat forming hydrocolloid films, mucoadhesive rectal and vaginal suppositories and fast dissolving tablets.

In yet another preferred aspect, the dosage forms of the present invention may include one or more emulsifiers, plasticizers, taste modifiers, coloring agents, preservatives, permeation enhancers, stabilizers, wetting agents, non-aqueous vehicles, lipid vehicles, metabolism inhibitors and buffering agents.

The present invention also provides a method for treating sexual dysfunction in an animal, preferably a mammal, more preferably a human, most preferably a human male; which method involves the administration of sildenafil citrate using a dosage form of the present invention which contains an effective amount of a sildenafil citrate/highly water soluble sugar solid dispersion.

The present invention also provides methods for making the dosage forms of the present invention. In a preferred aspect, the present invention provides a method for making the dosage forms, including: (a) mixing sildenafil citrate with a highly water soluble sugar, (b) heating the mixture of (a) to a temperature above the eutectic temperature for the mixture; (c) rapidly cooling the mixture to form a glassy solid; (d) optionally, size reducing the glassy solid; and (e) incorporating the size reduced solid into a dosage form or delivery system.

In another preferred aspect, the present invention provides a method for making dosage forms, including: (a) dispersing sildenafil citrate in a solvent; (b) microfluidizing the sildenafil citrate in solution, reducing the mean average particle size of the sildenafil citrate; (c) adding a highly water soluble sugar; (d) recovering a solid dispersion of sildenafil citrate and highly water soluble sugar; and, (e) incorporating the solid dispersion into a dosage form or delivery system.

The present invention also provides a mucoadhesive film dosage form including an effective dose of sildenafil citrate in a solid dispersion with xylitol, which solid dispersion is mixed with hydropolymer, a film forming reagent. The mucoadhesive films of the present invention will dissolve when applied to a mucosal surface. Preferably, the mucoadhesive films will dissolve within 10 to 600 seconds after being applied to a mucosal surface. More preferably, the mucoadhesive films will dissolve within 200 seconds after being applied to a

mucosal surface. Preferably, the solid dispersion incorporated into the mucoadhesive film dosage forms of the present invention will have a ratio of sildenafil citrate to highly water soluble sugar, more preferably mannitol, xylitol, sorbitol, or a mixture thereof, most preferably xylitol, of 19:1 to 1:19 on a mass basis; preferably 9:1 to 1:3; more preferably 9:1 to 1:1; most preferably 9:1.

Brief Description of the Drawing

There are shown in the drawings certain exemplary embodiments of the present invention as presently preferred. It should be understood that the present invention is not limited to the embodiments disclosed as examples, and is capable of variation within the spirit and scope of the appended claims.

In the drawings,

Figure 1 is an illustration depicting the preferred administration routes for the dosage forms of the present invention;

Figure 2 is an illustration depicting various mucosal delivery sites in the oral cavity for the dosage forms of the present invention;

Figure 3 is the structural formula for Sildenafil citrate;

Figure 4 is a graphical representation of the aqueous solubility profile for sildenafil citrate powder;

Figure 5 is a graphical representation of comparative aqueous solubility profiles for various sildenafil citrate compositions;

Figure 6 is a graphical representation of comparative release profiles of sildenafil citrate for sildenafil citrate tablets (Viagra®) and a mucosal surface-coat-forming film dosage form of the present invention in the form of an intraoral film;

Figure 7 is a graphical representation of comparative release profiles of sildenafil citrate for sildenafil citrate tablets (Viagra®) and a mucosal surface-coat-forming film dosage form of the present invention in the form of a mucoadhesive sublingual disc;

Figure 8 is a graphical representation of comparative pharmacokinetic profiles for sildenafil citrate tablets (Viagra®) and a mucosal surface-coat-forming film dosage form of the present invention in the form of a mucoadhesive sublingual disc;

Figure 9 is a graphical representation of comparative sildenafil citrate absorption kinetic profiles for sildenafil citrate tablets (Viagra®) and a mucosal surface-coat-forming film dosage form of the present invention in the form of a mucoadhesive device;

Figure 10 depicts of one manufacturing process for producing intraoral film dosage forms of the present invention; and,

Figure 11 depicts a packaging concept of the present invention.

Detailed Description

The products and methods of the present invention provide a means for increasing the water solubility and bioavailability of sildenafil citrate. More particularly the invention provides sildenafil citrate in highly water-soluble solid dispersions with certain highly water soluble sugars. The invention also provides methods of preparing such solid dispersions. The invention further provides methods for the preparation of highly water soluble sildenafil citrate dosage forms, for example, nasal/pulmonary administrations, fast dissolving dosage forms for oral and intra oral applications, and mucoadhesive dosage forms that can be administered, for example, lingually, sublingually, vaginally, and/or rectally. The dosage forms of the present invention enable the absorption of sildenafil citrate at the site of administration. The dosage forms of the present invention further facilitate the controlled release of sildenafil citrate. Finally, the invention provides a method of treating sexual dysfunction in an individual using dosage forms containing sildenafil citrate in a solid dispersion with a highly water soluble sugar.

Sildenafil citrate has the following chemical formula: 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate and the structural formula shown in **Figure 3**.

Highly water soluble sugars suitable for use with the present invention include mannitol, xylitol, sorbitol, sucrose, dextrose, galactose, lactose, fructose and maltose;

preferably, the highly water soluble sugar will be mannitol, xylitol, sorbitol or a mixture thereof; most preferably, the highly water soluble sugar will be xylitol.

Mannitol is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol is widely used in pharmaceutical formulations as a diluent, carrier, and plasticizer. Mannitol occurs as a white, odorless, crystalline powder, or free–flow granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Mannitol has a melting point of 167 °C and a water solubility of 180 mg/mL at room temperature. Mannitol is thermally stable at or around its melting point (Kanig, L. J. Pharm. Sci, 53, 188, 1964). Mannitol is freely water soluble, non–toxic, thermally stable, and pharmacologically inert. Mannitol is readily available from any number of commercial sources.

Sorbitol is a hexahydric alcohol also related to mannose and is isomeric with mannitol. Sorbitol is widely used as an excipient, diluent, plasticizer, and stabilizer in various pharmaceutical formulations. Sorbitol occurs as an odorless, white or almost colorless crystalline, hygroscopic powder. It has a pleasant, cooling, sweet taste and has approximately 50–60% the sweetness of sucrose. Sorbitol in its anhydrous form has a melting point of 111 °C and a water solubility of 2,000 mg/mL at room temperature. Sorbitol does not darken or decompose at elevated temperatures. Sorbitol is freely water soluble, non–toxic, thermally stable, and pharmacologically inert. Sorbitol is readily available from any number of commercial sources.

Xylitol is a pentahydric alcohol derived from xylose. Xylitol is widely used as non-cariogenic sweetening agent in tablets, syrups and coatings. Xylitol occurs as a white, granular solid comprising crystalline, equi-dimensional particles having a mean diameter of about 0.4 to 0.7 mm. It is odorless, with a sweet taste that imparts a cooling sensation. Xylitol in the stable form has a melting point of 94 °C and a water solubility of 625 mg/mL at room temperature. Xylitol is thermally stable at or around its melting point (Sirenius, I. Etc. Pharm. Sci, 68, 791, 1979). Xylitol is freely water soluble, non-toxic, thermally stable, and pharmacologically inert. Xylitol is readily available from any number of commercial sources.

Preferably, the solid dispersion of sildenafil citrate and highly water soluble sugar of the present invention will contain 5 to 95% by weight highly water soluble sugar; more

preferably the solid dispersion will contain 5 to 75% by weight highly water soluble sugar; most preferably the solid dispersion will contain 10 to 50% by weight highly water soluble sugar.

The sildenafil citrate/highly water soluble sugar solid dispersions of the present invention will preferably exhibit a water solubility of at least 20 mg/mL, more preferably at least 30 mg/mL, still more preferably at least 40 mg/mL, most preferably at least 50 mg/mL.

Preferably, the dosage forms of the present invention will contain a sildenafil citrate/highly water soluble sugar solid dispersion wherein the highly water soluble sugar is preferably mannitol, xylitol, sorbitol or a mixture thereof, most preferably, xylitol and wherein the mass ratio of sildenafil citrate to highly water soluble sugar in the solid dispersion is 19:1 to 1:19, more preferably 9:1 to 1:3, still more preferably 9:1 to 1:1, most preferably 9:1.

The dosage forms of the present invention may also optional include additional ingredients, including, but by no means limited to, permeation enhancing agents, taste modifying agents, emulsifying agents, plasticizing agents, buffering agents, coloring agents, stabilizing agents and preservatives.

Taste modifying agents suitable for use in the dosage forms of the present invention include, but are by no means limited to, flavoring agents, sweetening agents and taste masking agents. Preferred taste modifying agents include the essential oils or water soluble extracts of menthol, wintergreen, peppermint, sweet mint, spearmint, vanillin, cherry, chocolate, cinnamon, clove, lemon, orange, raspberry, rose, spice, violet, herbal, fruit, strawberry, grape, pineapple, peach, kiwi, papaya, mango, coconut, apple, coffee, plum, watermelon, nuts, durean, green tea, grapefruit, banana, butter, camomile, sugar, dextrose, lactose, mannitol, sucrose, xylitol, malitol, acesulfame potassium, talin, glycyrrhizin, sucralose, aspartame, saccharin, sodium saccharin, sodium cyclamate and honey.

Emulsifying agents suitable for use in the dosage forms of the present invention include, but are by no means limited to, solubilizers and wetting agents. Preferred emulsifying agents include polyvinyl alcohol, sorbitan esters, cyclodextrins, benzyl benzoate, glyceryl monostearate, polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamer,

polyoxyethylene castor oil derivatives, hydrogenated vegetable oils, bile salts, polysorbates and ethanol.

Plasticizing agents suitable for use in the dosage forms of the present invention include, but are by no means limited to, glycerin, sorbitol, propylene glycol, polyethylene glycol, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters.

Buffering agents suitable for use in the dosage forms of the present invention include, but are by no means limited to, acidulants and alkalizing agents. Preferred buffering agents include citric acid, fumaric acid, lactic acid, tartaric acid, malic acid, sodium citrate, sodium bicarbonate, sodium carbonate, sodium phosphate, potassium phosphate and magnesium oxide.

Coloring agents suitable for use in the dosage forms of the present invention include, but are by no means limited to, FD & C coloring agents, natural coloring agents, natural juice concentrates and pigments. Preferred pigments include titanium oxide, silicon dioxide and zinc oxide.

Stabilizers suitable for use in the dosage forms of the present invention include, but are by no means limited to, anti-oxidants, chelating agents and enzyme inhibitors. Preferred stabilizers include ascorbic acid, vitamin E, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, dilauryl thiodipropionate, thiodipropionic acid, gum guaiac, citric acid, edetic acid and its salts and glutathione.

Preservatives suitable for use in the dosage forms of the present invention include, but are by no means limited to, anti-microbial agents and non-organic compounds. Preferred preservatives include sodium benzoate, parabens and derivatives, sorbic acid and its salts, propionic acids and its salts, sulfur dioxide and sulfites, acetic acid and acetates, nitrites and nitrates.

The sildenafil citrate/highly water soluble sugar solid dispersions of the present invention are preferably produced using one of three approaches, namely, by a fusion (hot melt) process, by a solvent process or by a combination of both. The basic processes for preparing solid dispersions (i.e. hot melt, solvent, ...) are well known in the art. For example see Chiou, J. PHARM. SCI., vol. 60, No. 9, 1281 (1971); Ford, PHARM. ACTA HELV. 61, No.

3 (1986) and Bloch, PHARM. ACTA HELV. 61, No. 3 (1986); which are incorporated herein by reference.

The fusion (hot melt) process suitable for use in making the sildenafil citrate/highly water soluble sugar solid dispersion of the present invention for incorporation into the dosage forms of the present invention, involves: (a) mixing sildenafil citrate with a highly water soluble sugar, (b) heating the mixture of (a) to a temperature in excess of the eutectic temperature for the mixture of (a), (c) rapidly cooling the mixture to form a glassy solid, (d) optionally, size reducing the glassy solid, and (e) incorporating the size reduced solid into a dosage form.

The highly water soluble sugars preferably used in the fusion (hot melt) process of the present invention are mannitol, xylitol, sorbitol and mixtures thereof. For illustrative purposes, the fusion (hot melt) process will be discussed in greater detail herein below using the most preferred highly water soluble sugar of the present invention, xylitol.

First, sildenafil citrate is physically mixed with xylitol. The mixture is then heated preferably to a temperature of at least 190°C, most preferably to a temperature in the range of 190 to 195 °C, to co-melt the xylitol and sildenafil citrate at above the eutectic temperature for the mixture. Alternatively, a small amount of a liquid solvent (5 to 10% w/w) can preferably be added into the sildenafil citrate/xylitol mixture to facilitate the use of a lower melt temperature. Suitable liquid solvents include water; alcohols including for example: methanol, ethanol, isopropanol and butanol; and glycols including for example: polyethylene glycol, propylene glycol and glycerol. This small amount of solvent can be subsequently removed during the cooling/solidification of the co-melt.

The co-melted liquid is then rapidly cooled, preferably using a heat transfer element or surface at about -70°C, to provide a supersaturated solid mixture of sildenafil citrate in xylitol. More specifically, the co-melted liquid is preferably cooled until solidified at a rate of at least between 10 to 500 °C/sec, more preferably at least 5 to 250 °C/sec; most preferably at least 100 °C/sec. The co-melted liquid may preferably be cooled by spreading the mixture onto cold stainless steel plates to help facilitate rapid heat loss. The co-melted liquid may also be cooled using an ultra-freezer. Most preferably, the co-melted liquid is spray-congealed using a modified spray drier and spraying the mixture into a cooling medium, such as liquid nitrogen, nitrogen gas in a cooling chamber or spraying the mixture onto cold

stainless steel plates. The use of spray-congealing to rapidly cool and solidify the mixture of sildenafil citrate and xylitol is most preferred because the pellets of sildenafil citrate/xylitol solid dispersion can be obtained thereby without the need for further size reduction, which further size reduction can inadvertently result in an alteration of the crystalline structure of the sildenafil citrate in the solid dispersion. Alternatively, the sildenafil citrate/xylitol solid dispersion obtained from the rapid cooling of the co-melted liquid can be size reduced using known size reduction methods.

Preferably, the fusion (hot melt) process can be carried out in a continuous or semi-continuous operation. For example, a hot melt extruder can be used to facilitate such continuous or semi-continuous processing. That is, for instance, sildenafil citrate and xylitol powders can be automatically fed into a twin screw hot melt extruder from a hopper. The twin screw hot melt extruder may have multiple heating zones to feed, mix, knead, and melt the mixture of sildenafil citrate and xylitol powders. The co-melt liquid or semi-liquid can then be extruded through a ribbon die to form a thin film or through a rod die to form thin strings. The extruded liquid, films or strings can preferably be immediately chilled and solidified by dropping them into liquid nitrogen, onto cold stainless steel plates, into liquid/solid carbon dioxide, or onto a conveyor or belt which passes into an ultra low freezer. The solidified dispersion obtained can subsequently be ground into powder and fromulated into various dosage forms.

The solvent process suitable for use in making the sildenafil citrate/highly water soluble sugar solid dispersions of the present invention comprises: (a) mixing sildenafil citrate in a solvent with agitation; (b) adding a highly water soluble sugar to the mixture of (a) with continued agitation; (c) spray-drying the mixture of (b); and (d) incorporating the spray-dried product into a dosage form. The primary advantage of using the solvent process is that there is a reduced likelihood of thermal decomposition of sildenafil citrate or of the highly water soluble sugar. The solvent process is hindered, however, by the potential for residual solvent remaining in the product solid dispersion following processing.

The mixing of the sildenafil citrate with the solvent and the highly water soluble sugar in the solvent process is preferably accomplished using a microfluidizer. In the initial mixing of sildenafil citrate and the solvent, the agitation preferably operates to size reduce the

average particle size of the sildenafil citrate in solution, most preferably, the sildenafil citrate is reduced to an average particle size of 2 μm or less.

Solvents suitable for use in the solvent process of the present invention include aqueous solutions and alcoholic solutions, preferably aqueous solutions, most preferably water.

Highly water soluble sugars used in the solvent process of the present invention are, preferably, mannitol, xylitol, sorbitol or mixtures thereof, most preferably xylitol. The highly water soluble sugar is gradually added into the mixture in (b). The mixture is continually agitated throughout (a) and (b), preferably using a microfluidizer to facilitate the dissolution of the sildenafil citrate into the highly water soluble sugar.

The solvent is eventually removed from the sildenafil citrate/highly water soluble sugar solution using any suitable technique, preferably evaporation, spray-drying or freeze-drying techniques, most preferably using spray-drying techniques.

The present invention further provides methods for treating sexual dysfunction in a subject, preferably a human, most preferably a male human; including administering a dosage form of the present invention to the subject, which dosage form contains a solid dispersion of sildenafil citrate and a highly water soluble sugar, preferably mannitol, xylitol, sorbitol or a mixture thereof, more preferably xylitol. A preferred method for treating sexual dysfunction in a subject including administering a dosage form containing a sildenafil citrate/xylitol solid dispersion, more preferably, a sildenafil citrate/xylitol solid dispersion having a sildenafil citrate to xylitol ratio of 9:1 to 3:1 on a mass basis, most preferably 9:1.

The sildenafil citrate/highly water soluble sugar solid dispersions of the present invention significantly increase the water solubility of sildenafil citrate, preferably, the sildenafil citrate/highly water soluble sugar solid dispersions of the present invention will exhibit a sildenafil citrate water solubility 10 to 15 times greater than that of sildenafil citrate alone, see **Figures 4** and **5** and **Table 1**. The sildenafil citrate/highly water soluble sugar solid dispersions of the present invention also exhibit a resistance to aggregation and agglomeration. The sildenafil citrate/highly water soluble sugar solid dispersions of the present invention further exhibit favorable wettability and dispersibility characteristics in aqueous solution. The increased water solubility of sildenafil citrate exhibited by the

sildenafil citrate/highly water soluble sugar solid dispersions of the present invention provide for an increase in the oral bioavailability of sildenafil citrate for use in regular oral dosage forms or in fast dissolving intraoral delivery systems. Additionally by increasing the bioavailability of sildenafil citrate, the sildenafil citrate/highly water soluble sugar solid dispersions of the present invention facilitate a reduction in the sildenafil citrate unit dose necessary to achieve the desired pharmocologic effect. It is believed that the use of lower unit doses of sildenafil citrate will reduce the occurrence and/or severity of side effects. Also, use of lower unit doses of sildenafil citrate will result in reduced raw material costs for producing sildenafil citrate dosage forms.

Table 1: Water solubility of a sildenafil citrate/xylitol solid dispersion having the noted mass ratio of sildenafil citrate to xylitol

	Sildenafil citrate/Xylitol Solid Dispersion					
Mass Ratio	10:0	9:1	3:1	1:1	1:3	1:9
Solubility* (mg/mL)	2.49	30.82	38.47	53.56	48.88	1.10

* 4 hour solubility

The high water solubility of the sildenafil citrate/sugar solid dispersion of the present invention facilitates the incorporation of sildenafil citrate into heretofore impractical dosage forms having rapid absorption, which dosage forms by–pass first–pass metabolism and/or provide rapid onset of therapeutic action both of which are highly desired for this class of medication. Specifically, the sildenafil citrate/highly water soluble sugar solid dispersions of the present invention can be formulated into a wide variety of dosage forms having high sildenafil citrate water solubility, fast dissolution, rapid absorption, quick onset of therapeutic action, improved bioavailability, lower dose regimens, and reduced occurrence and/or severity of unwanted side effects, see **Table 2** and **Figures 4** and **5**.

Table 2: Formulation Examples

Composition	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7
Sildenafil citrate	5%	63%	63%	56.2%	52.2%	60%	20%
Xylitol	5%	7%	7%	6.2%	5.8%	6.67%	20%
Benzoic acid	0.01%		0.01%	0.013%	0.05%	0.05%	
Propylene glycol	1%		8%	13.4%	4%	9%	
EDTA	2%		0.01%	2.7%	0.5%	3%	
Poloxamer L–44	1%		5%	4.5%			
Carbopol	1%						
Methocel E15			10%	8.9%		10%	
Methocel E50					20%	10%	
Sod. bicarbonate		25%					
Cremophor RH–40			1%				
Polypro 5000			2%				
Aspartame		1%	1%	5.4%			
Peppermint oil		1%	1%		1.3%		
Orange oil				2.6%			
MagnaSweet 100		1%			11%		
NaCl					0.5%		
Lemon					2.34%		
Vanilla extract		1%			1.3%		
Vanillin				0.09%			
Water	84%	1%	2%		1%	2%	
Mannitol							40%
Na Croscamellose							20%

*% is weight by weight

For example, a sildenafil citrate/xylitol solid dispersion of the present invention was formulated into two dosage forms, namely, an intraoral dissolving film and a mucoadhesive disc, which can be administered sublingually, rectally, and/or vaginally. The dissolution profiles for the intraoral dissolving films containing the sildenafil citrate/xylitol solid dispersion of the present invention are shown in **Figures 6** and **7**. As may be seen from these figures, the sildenafil citrate intraoral dissolving films of the present invention exhibit rapid disintegration and dissolution profiles.

A zero-order release rate was observed for the mucoadhesive discs containing the sildenafil citrate/xylitol solid dispersion of the present invention, as shown in **Figure 7**.

Solubility profiles for various other dosage forms incorporating sildenafil citrate/highly water soluble sugar solid dispersions of the present invention are presented in **Figures 5**.

It should be noted that the saturated solubility of sildenafil citrate powder is only about 3.5 mg/mL. A sildenafil citrate/xylitol solid dispersion of the present invention with a sildenafil citrate to xylitol mass ratio of 9:1 exhibits a sildenafil citrate water solubility of 30 mg/mL. Contrastingly, the solubility of sildenafil citrate directly formulated into film tablets exhibited a water solubility of only 7 mg/mL.

Accordingly, dosage forms suitable for use with the current invention include mucoadhesive nasal sprays, effervescent tablets, mucoadhesive sublingual discs, mucosal surface-coat forming hydrocolloid films, mucoadhesive rectal and vaginal suppositories and fast dissolving tablets. Preferably, the dosage forms should provide a non-invasive, effective and economic means to deliver sildenafil citrate to a given target site.

A preferred dosage form of the present invention is a water soluble, mucosal surface-coat-forming film (hereinafter "film"). Preferably, these films will contain hydrocolloid and may optionally further contain any one or more of the following: an emulsifying agent, a plasticizing agent, a taste modifying agent, a preservative, a buffering agent, a coloring agent, a permeation enhancing agent and a stabilizing agent. These agents are exemplified, as described herein above. The preferred percentage on a dry weight basis of single ingredients incorporated into the film dosage forms of the present invention in each of the following categories are: emulsifying agent (0.1%-10%), plasticizing agent (0.5-20%), taste modifying agents (0.1-10%), coloring agents (0.01-5%), preservatives (0.01-10%), buffering agents (0.1-10%) and stabilizers (0.01-5%).

Delivery of active agents in solid form via the mouth causes problems to patients who may choke on the dosage unit. This effect is caused at least in part by the mobility of the dosage unit within the mouth. The film dosage forms of the present invention are not mobile in the mouth because on contact with the moist mucosal surface, the film becomes a coating that adheres to the mucosal surface and then disintegrates and dissolves over a time frame controlled by the design of the film. The film, in a preferred embodiment of the present invention, is a flexible, non-tacky, dry conveniently packaged dosage form. Once removed from the package and placed on a mucosal surface, the film hydrates substantially immediately to form a coating on the moist surface of the mucous membrane and then disintegrates and dissolves to release sildenafil.

The film may release the sildenafil over a period of time that is determined by a number of different factors. These factors include the dimensions of the film, the concentration of the sildenafil citrate/highly water soluble sugar solid dispersion present in the film, the solubility of the sildenafil citrate/highly water soluble sugar solid dispersion at the mucosal surface and how the dispersion is dispersed throughout the film. The thickness of the film is a factor in determining the rate of dissolution. A thick film will dissolve more slowly than an otherwise similar thin film. The surface area of a film can be adjusted up to about 5 square centimeters. Solubilizing agents that are well known in the art may be included in the film. The extent of uptake of the sildenafil from the film at the mucosal surface can be controlled by the dissolution rate of the film. A fast dissolving film will release the sildenafil and this in turn may cause the sildenafil to be swallowed and be taken up in the gastrointestinal tract. In contrast, a slow dissolving film will give rise to increased uptake by the mucosal surface. A further parameter governing the release of the sildenafil at the mucosal surface is the manner in which the sildenafil citrate/highly water soluble sugar solid dispersion is dispersed in the film. For example, the sildenafil citrate/highly water soluble sugar solid dispersion may be dispersed as colloidal particles or microencapsulated within the film or alternatively may be mixed throughout the film as a reagent during casting.

The film dosage forms of the present invention may be administered to the subject by placing the film on a mucosal surface, at which time the film becomes a mucoadhesive coating, characterized by the property that it can no longer exist in an independent form and is subsequently dispersed in solution.

The release of sildenafil from the film dosage forms of the present invention occurs without mastication or the need for intake of water.

The mechanical properties of the film are determined by tensile strength modulus, percent elongation (ASTM D882, standard test method for tensile properties of thin plastic sheet) and tear propagation resistance (ASTM D1938, standard test method for tear propagation resistance of plastic film and thin sheet by single tear method). The mechanical properties are measured herein using standard protocols as described in Annual Book of ASTM Standards, American National Standards Institute, NY 1995.

A factor that plays a significant role in determining the properties of the film dosage form compositions of the present invention is the viscosity of the hydrocolloid used in

making the film. The viscosity of the hydrocolloid depends on its molecular size, derivation, hydrophobicity and hydrophilicity and the presence of other additives in the formulation.

Preferably, the hydrocolloid concentration in the film dosage forms of the present invention will be in the range of 5 to 99% of the dry weight of the film, more preferably greater than 10%. These films have a dry tack and a wet tack which facilitates an improved ease of handling and use. The low dry tack properties of the film dosage forms of the present invention provide for a physically attractive and easily handled film that is neither fragile nor sticky and can be easily removed from the dosage form packaging and placed on a suitable mucosal surface. The wet tack properties of the film dosage forms of the present invention provide the advantage of stickiness of the moistened film such that when the film is placed on the mucosa, the film will remain attached at the site until the film dissolves. In contrast, if the wet tack is too low, the film could move in the mouth and be inadvertently swallowed before completely dissolving, presenting a potential choking hazard. Furthermore, the low moisture content and low dry tack of the film dosage forms of the present invention enhance the shelf life of the films and the flexibility of the dosage forms. These properties render the film dosage forms of the present invention suitable for easy manufacture, packaging, storage, handling and use.

Preferably, the film dosage forms of the present invention may contain a water soluble polymer, which preferably has a gelation temperature greater than 70°C for 2% polymer solution. The hydration rate of a hydrocolloid having these features is rapid with a percentage moisture absorption of polymers in the range of 5-20% at 75% humidity at room temperature. The hydration rate is selected according to the desired wettability of the film dosage forms of the present invention thereby obviating the need for surfactants. The wet tack of the hydrated film dosage forms of the present invention preferably ranges from 35 to 150 grams, more preferably 40 to 100 grams. The percentage swelling is preferably less than 10% within 60 seconds. The film dosage forms of the present invention are preferably casted to have a thickness of 1 to 20 mil. The water content of the film dosage forms of the present invention preferably ranges from 0.5 to 10% with a more preferred range of 1 to 5%.

Preferably, the film dosage forms of the present invention may be formed using a mixture of two or more types of the same hydrocolloid that differ only in molecular weights and/or different degrees of substitution. The time of dissolution of the film dosage forms of

the present invention are preferably in the rage of 10 to 600 seconds, the time of disintegration is preferably 1 to 300 seconds.

Ease of handling of the film dosage forms of the present invention is characterized by the dry tack of the film and the flexibility is reflected by the tensile strength, modulus, % elongation and tear resistance of the film. For example, the dry tack is preferably in the range of 0.2 to 3.5 grams, more preferably 0.4 to 2.0 grams. The tensile strength is preferably in the range of 1,500 to 10,000 psi; more preferably 2,000 to 8,000 psi; most preferably greater than 2,000 psi. The modulus is preferably in the range from 35,000 to 300,000. For a film having a thickness of 2 mil, the % elongation is preferably less than 20%, more preferably between 1 to 10%.

Hydrocolloids suitable for use in the film dosage forms of the present invention include water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan, carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from *aloe*, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamaring gum, oat gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac and *rhizobium* gum.

Alternatively, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. Preferably, the hydrocolloid will include hydroxpropyl methyl cellulose with a methoxy content of about 19 to 30% and

hydroxypropyl content of 7 to 12% and a molecular weight of approximately 50,000 to 250,000 daltons.

The mucosal surface-coat-forming films of the present invention may exhibit any of the following features: a dry film thickness in the range of 1 to 20 mils, preferably less than 10 mils; a dry tack value of less than 3.5 g, preferably less than 2 g; a wet tack value of greater than 35 g; a tensile strength greater than 1500 psi; a modulus in the range of 35,000 to 300,000 psi; a tear propagation resistance in the range 0.001 to 1 N; a disintegration time in the range from 1 to 300 seconds; a dissolution time in the range from 10 to 600 seconds; and a percentage elongation of less than 20%.

A preferred method for preparing the mucosal surface-coat-forming film dosage forms of the present inventions involves: (a) dissolving a hydrocolloid in a solvent so as to form a substantially homogeneous preparation; (b) adding a sildenafil citrate/highly water soluble sugar solid dispersion of the present invention to the hydrocolloid preparation; (c) optionally adding an emulsifier, a plasticizer, a taste modifier, a coloring agent, a preservative, a permeation enhancer, a stabilizer and/or a buffering agent to the preparation; and (d) forming a mucosal surface-coat-forming film from the preparation. The method may optionally include (e) coating the mucosal surface-coat-forming film onto a backing film. The reagents may be combined in any order in a vessel having a heating source and a mixing device. The film forming step may preferably be performed using a dry extrusion process. This and other methods for preparing the film dosage forms of the present invention are set forth in greater detail in copending U.S. Patent Application Serial No. 09/434,878, filed November 5, 1999, the disclosure of which is incorporated herein by reference in its entirety.

The film dosage forms of the present invention can be prepared for use by selecting a film that is capable of delivering an effective dose and administering the film to the subject by placing it on a mucosal surface such as the oral mucosa, see **Figure 2**, where it dissolves in the body fluid for example, saliva and is swallowed in liquid form. **Figure 6** graphically represents the release profiles of mucosal surface-coat-forming film dosage forms of the present invention discussed in Examples 3 and 5 in comparision to that of a conventional sildenafil citrate film tablet (Viagra®). **Figure 7** shows the release profile of the mucoadhesive dosage forms of the present invention discussed in Examples 4 and 5 in comparison to that of a conventional sildenafil citrate film tablet (Viagra®). The fraction of

the dose absorbed through the mucosal tissue can be increased by incorporating a permeation enhancer in the film dosage forms of the present invention.

The film dosage forms of the present invention exhibit an overall bioavailability greater than that associated with conventional oral tablets. Specifically, the film dosage forms of the present invention provide an overall bioavailability of the sildenafil which is absorbed both locally at the mucous membrane and systemically within the gastrointestinal system greater than that exhibited by the same dose of sildenafil administered by a conventional oral table or capsule dosage form. This is exemplified in **Figure 8** and **Table 3** which show the improved bioavailability of sildenafil from the film dosage form of the present invention compared to a conventional sildenafil citrate film tablet (Viagra®). **Table 4** lists the estimated pharmocokinetic parameters for the film dosage form of the present invention as compared to a conventional sildenafil citrate film tablet (Viagra®). The oral bioavailability of sildenafil was increased 25% compared with the conventional sildenafil citrate film tablet (Viagra®).

Table 3: Pharmacokinetic comparison for a sildenafil citrate/xylitol solid dispersion containing mucosal surface-coat-forming film dosage form of the present invention and a sildenafil citrate film tablet (Viagra®)

Parameters	Ex. 4 (S)	Viagra® (V)	Ratio S/V	Power
AUC* (0-t)	365.5	293.1	1.247	0.86
AUC (inf)	378.0	310.4	1.218	0.88
C_{max} (ng/mL)	109.9	106.8	1.029	0.15
T_{max} (h)	1.00	1.00	1.00	0.08
K_e (1/h)	0.354	0.285	1.245	0.32
$T_{½}$ (h)	1.99	2.56	0.775	0.23

*Area under the curve

Table 4: Estimated pharmacokinetic parameters for a sildenafil citrate/xylitol solid dispersion containing mucosal surface-coat-forming dosage form of the present invention and sildenafil citrate film tablet (Viagra®)

Parameters	Ex. 4	Viagra®
V/F	206.47	251.69
K_a (1/h)	2.42	4.99
K_e (1/h)	0.317	0.247
$T_{1/2}$ (h)	2.186	2.805
T_{lag} (h)	0.269	0.375
F(%)	50.85	41.51
T_{max} (h)	1.265	1.009
C_{max}	88.3	84.9

The oral retention characteristics, mouth feel properties, flavor and taste of the film dosage forms of the present invention can preferably be modified based on the hydrocolloid and other excipients used to prepare the films and medications.

Examples

The preferred embodiments of the present invention will now be further described through the following examples set forth hereinbelow which are intended to be illustrative of the preferred embodiments of the present invention and are not intended to limit the scope of the invention as set forth in the appended claims.

Example 1: Sildenafil citrate mucoadhesive nasal spray

A mucoadhesive nasal spray dosage form of the present invention was prepared using a solid dispersion of sildenafil citrate and xylitol wherein the mass ratio of sildenafil citrate to xylitol was 1:1. The sildenafil citrate and xylitol were comelted at 195 °C and solidified rapidly in an ultra-low freezer. After completely solidified, the solid was ground into fine powder. The fine powder was completely dissolved in water. Carbopol was added into the aqueous solution to serve as a mucoadhesive agent to increase the residence time of the sildenafil citrate in the nasal cavity after spraying. Propylene glycol and EDTA were also added to the nasal spray dosage form to act as absorption enhancers. Benzoic acid was added to the nasal spray dosage form as a preservative.

Example 2: Sildenafil citrate effervescent tablet

An effervescent tablet dosage from of the present invention was prepared using a solid dispersion of sildenafil citrate and xylitol wherein the mass ratio of sildenafil citrate to xylitol was 9:1. The sildenafil citrate and xylitol were comelted at 195 °C and subsequently solidified by rapid cooling in an ultra-low freezer. The product solid was ground into fine powder. The sildenafil citrate/xylitol solid dispersion powder was well mixed with sodium bicarbonate and flavoring agents. The mixture was compressed into tablets.

Example 3: Fast dissolving intraoral film

A mucosal surface-coat-forming film dosage form of the present invention in the form of a fast dissolving intraoral film was prepared using a solid dispersion of sildenafil citrate and xylitol wherein the mass ratio of sildenafil citrate to xylitol was 9:1. The sildenafil citrate and xylitol were comelted at 195 °C and subsequently solidified by rapid cooling in an ultra-low freezer. The product solid was ground into fine powder. The sildenafil citrate/xylitol solid dispersion powder, flavoring agents, propylene glycol (plasticizer), preservatives, poloxamer and water–soluble polymer (Methocel) were all dissolved in water. Ethanol was added into the solution to reduce the surface tension, eliminate foam formation and accelerate degassing. The viscous solution was degassed in a vacuum chamber. The homogenous solution was then used to cast and form an intraoral film dosage form with a dry thickness of 3.2 mil.

Example 4: Mucoadhesive sublingual disc

A mucoadhesive sublingual disc dosage form of the present invention was prepared using a sildenafil citrate/xylitol solid dispersion wherein the sildenafil citrate to xylitol mass ration was 9:1 ratio. The sildenafil citrate and xylitol were comelted at 195 °C and subsequently solidified by rapid cooling in an ultra-low freezer. The product solid was ground into fine powder. The sildenafil citrate/xylitol solid dispersion powder, flavoring agents, propylene glycol (plasticizer), preservatives, poloxamer and water–soluble polymer (Methocel) were dissolved in water. Ethanol was added into the solution to reduce the surface tension, eliminate foam formation and accelerate degassing. The viscous solution was degassed in a vacuum chamber. The homogenous solution was used to cast and form a mucoadhesive sublingual disc (16 mil).

Example 5: Mucoadhesive sublingual disc and lingual film

Mucosal surface-coat-forming film dosage forms of the present invention in the form of a mucoadhesive sublingual disc and a lingual film were prepared using a sildenafil citrate/xylitol solid dispersion wherein the sildenafil citrate to xylitol mass ratio was 9:1. The sildenafil citrate and xylitol were comelted at 195 °C and subsequently solidified by rapid cooling in an ultra-low freezer. The product solid was ground into fine powder. The sildenafil citrate/xylitol solid dispersion powder, flavoring agents, propylene glycol (plasticizer), preservatives, and water–soluble polymer (Methocel) were dissolved in water. Ethanol was added into the solution to reduce its surface tension, eliminate foam formation and accelerate degassing. The viscous solution was degassed in a vacuum chamber. The homogenous solution was used to cast and form mucoadhesive sublingual discs (16 mil) and lingual films (3.5 mil).

Example 6: Mucoadhesive rectal or vaginal device

Mucoadhesive rectal/vaginal dosage forms of the present invention were prepared using a sildenafil citrate/xylitol solid dispersion with a sildenafil citrate to xylitol mass ration of 9:1. The sildenafil citrate and xylitol were comelted at 195 °C and subsequently solidified by rapid cooling in an ultra-low freezer. The product solid was then ground into fine powder. The sildenafil citrate/xylitol solid dispersion powder, propylene glycol (plasticizer), preservatives, and water–soluble polymer (Methocel) were dissolved in water. Ethanol was added into the solution to reduce its surface tension, eliminate foam formation and accelerate degassing. The viscous solution was degassed in a vacuum chamber. The homogenous solution was used to cast and form mucoadhesive devices (15 mil) for rectal and/or vaginal applications.

Example 7: Fast dissolving tablet

A fast dissolving tablet dosage form of the present invention was prepared using a sildenafil citrate/xylitol solid dispersion with a sildenafil citrate to xylitol ratio of 1:1. The sildenafil citrate and xylitol were comelted at 195 °C and subsequently solidified by rapid cooling in an ultra-low freezer. The product solid was ground into a fine powder. The sildenafil citrate/xylitol solid dispersion powder, mannitol, and sodium Croscamellose were kneaded together and molded into fast dissolving tablets after adding a small amount of water.

The present invention having been disclosed in connection with the foregoing embodiments, additional embodiments will now be apparent to persons skilled in the art. The present invention is not intended to be limited to the embodiments specifically mentioned, and accordingly reference should be made to the appended claims rather than the foregoing discussion, to assess the spirit and scope of the present invention in which exclusive rights are claimed.

We claim:

1. A dosage form comprising sildenafil citrate and a highly water soluble sugar.

2. The dosage form of claim 1, wherein the sildenafil citrate and the highly water soluble sugar form a solid dispersion.

3. The dosage form of claim 2, wherein the highly water soluble sugar is selected from the group consisting of mannitol, xylitol, sorbitol, sucrose, dextrose, galactose, lactose, fructose and maltose.

4. The dosage form of claim 2, wherein the highly water soluble sugar is mannitol.

5. The dosage form of claim 2, wherein the highly water soluble sugar is xylitol.

6. The dosage form of claim 2, wherein the highly water soluble sugar is sorbitol.

7. The dosage form of claim 2, wherein the dosage form is a mucoadhesive nasal spray.

8. The dosage form of claim 2, wherein the dosage form is an effervescent tablet.

9. The dosage from of claim 2, wherein the dosage form is a mucoadhesive sublingual disc.

10. The dosage form of claim 2, wherein the dosage form is a mucosal surface-coat forming hydrocolloid film.

11. The dosage form of claim 2, wherein the dosage form is a mucoadhesive suppository.

12. The dosage form of claim 11, wherein the dosage form is a mucoadhesive rectal suppository.

13. The dosage form of claim 11, wherein the dosage form is a mucoadhesive vaginal suppository.

12. The dosage form of claim 2, wherein the dosage form is a fast dissolving tablet.

13. The dosage form of claim 2, wherein the solid dispersion has a water solubility of at least 20 mg/ml.

14. The dosage form of claim 2, wherein the solid dispersion has a water solubility of at least 30 mg/ml.

15. The dosage form of claim 2, wherein the solid dispersion has a water solubility of at least 40 mg/ml.

16. The dosage form of claim 2, wherein the solid dispersion has a water solubility of at least 50 mg/ml.

17. The dosage form of claim 2, wherein the highly water soluble sugar comprises 5 to 95% of the solid dispersion by weight.

18. The dosage form of claim 2, wherein the highly water soluble sugar comprises 5 to 75% of the solid dispersion by weight.

19. The dosage form of claim 2, wherein the highly water soluble sugar comprises 10 to 50% of the solid dispersion by weight.

20. The dosage form of claim 5, wherein the ratio of sildenafil citrate to xylitol 19:1 to 1:19 on a mass basis.

21. The dosage form of claim 5, wherein the ratio of sildenafil citrate to xylitol is 9:1 to 1:3 on a mass basis.

22. The dosage form of claim 5, wherein the ratio of sildenafil citrate to xylitol is 9:1 to 1:1 on a mass basis.

23. The dosage form of claim 5, wherein the ratio of sildenafil citrate to xylitol is 9:1 on a mass basis.

24. The dosage form of claim 2, wherein the dosage form further comprises at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a coloring agent, a preservative, a permeation enhancer, a stabilizer, a wetting agent, a non-aqueous vehicle, a lipid vehicle, a metabolism inhibitor and a buffering agent.

25. A method of treating sexual dysfunction in an individual, comprising administering to the individual the dosage form of claim 2.

26. The method of claim 25, wherein the individual is a male.

27. A method of treating sexual dysfunction in an individual, comprising administering to the individual the dosage form of claim 21.

28. The method of claim 27, wherein the individual is a male.

29. A method of making the dosage form of claim 2, comprising:

(a) mixing sildenafil citrate and a highly water soluble sugar;

(b) heating the mixture of (a) to a temperature above the eutectic temperature for the mixture;

(c) rapidly cooling the mixture to form a glassy solid;

(d) size reducing the glassy solid;

(e) incorporating the size reduced solid into the dosage form.

30. The method of claim 29, wherein the highly water soluble sugar is xylitol and wherein the mixture is heated to at least 190°C in (b).

31. The method of claim 29, further comprising the addition of a liquid to the mixture of (a), wherein the liquid is selected from the group consisting of water, alcohols and glycols.

32. A method of making the dosage form of claim 2, comprising:

(a) mixing sildenafil citrate and a highly water soluble sugar;

(b) heating the mixture of (a) to a temperature above the eutectic temperature for the mixture;

(c) rapidly cooling the mixture by spray-congealing to form pellets of sildenafil citrate/highly water soluble sugar solid dispersion;

(d) incorporating the pellets into the dosage form.

33. The method of claim 32, wherein the highly water soluble sugar is xylitol and wherein the mixture is heated to at least 190°C in (b).

34. The method of claim 32, further comprising the addition of a liquid to the mixture of (a), wherein the liquid is selected from the group consisting of water, alcohols and glycols.

35. A method of making the dosage form of claim 2, comprising:

(a) dispersing sildenafil citrate in an aqueous solvent;

(b) microfluidizing the sildenafil citrate in solution to reduce the particle size of the sildenafil citrate;

(c) adding a highly water soluble sugar;

(d) recovering a solid dispersion of sildenafil citrate and highly water soluble sugar; and,

(e) incorporating the solid dispersion into a delivery system.

36. The method of claim 35, wherein (d) comprises spray drying or freeze drying the solid dispersion.

37. A dosage form comprising a mucoadhesive film comprising an effective dose of sildenafil citrate, wherein the sildenafil citrate forms a solid dispersion with xylitol, wherein the solid dispersion is mixed with a film forming reagent comprising a hydropolymer and wherein the mucoadhesive film dissolves when applied to a mucosal surface.

38. The dosage form of claim 37, wherein the dosage form dissolves within 10 to 600 seconds after being applied to a mucosal surface.

39. The dosage form of claim 37, wherein the dosage form dissolves within 200 seconds after being applied to a mucosal surface.

40. The dosage form of claim 39, wherein the ratio of sildenafil citrate to xylitol is 19:1 to 1:19 on a mass basis.

41. The dosage form of claim 39, wherein the ratio of sildenafil citrate to xylitol is 9:1 to 1:3 on a mass basis.

42. The dosage form of claim 39, wherein the ratio of sildenafil citrate to xylitol is 9:1 to 1:1 on a mass basis.

43. The dosage form of claim 39, wherein the ratio of sildenafil citrate to xylitol is 9:1 on a mass basis.

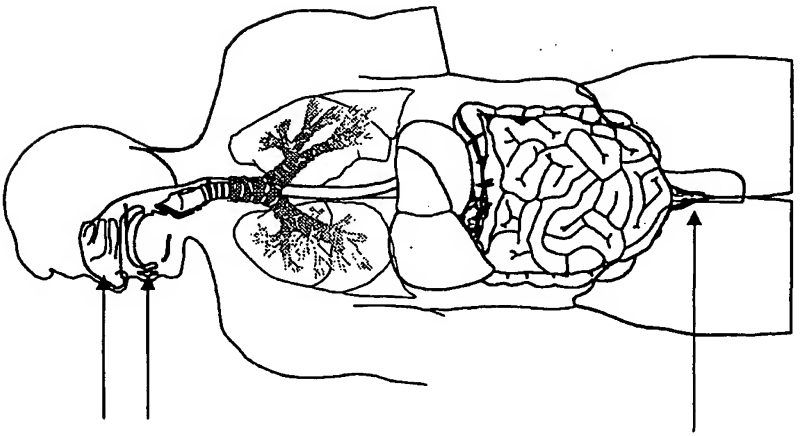
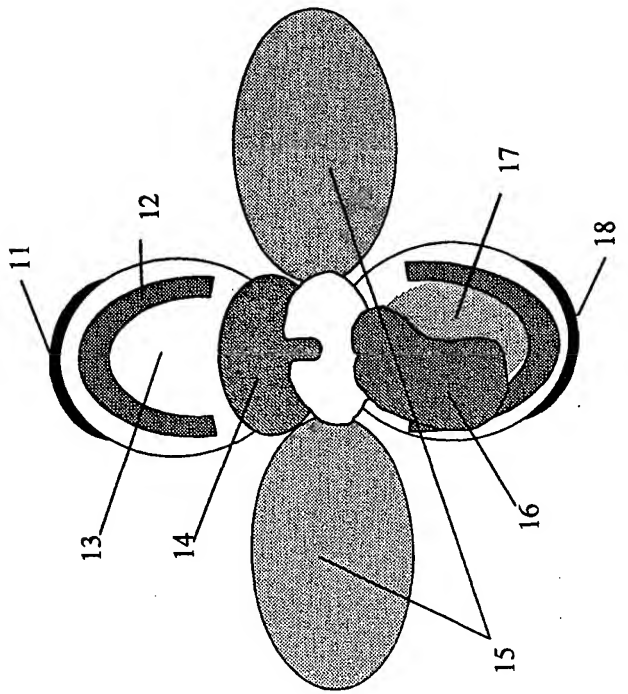


FIG. 1



11 - upper lip
12 - gingiva
13 - hard palate
14 - soft palate
15 - cheek
16 - lingual
17 - sublingual
18 - lower lip

FIG. 2

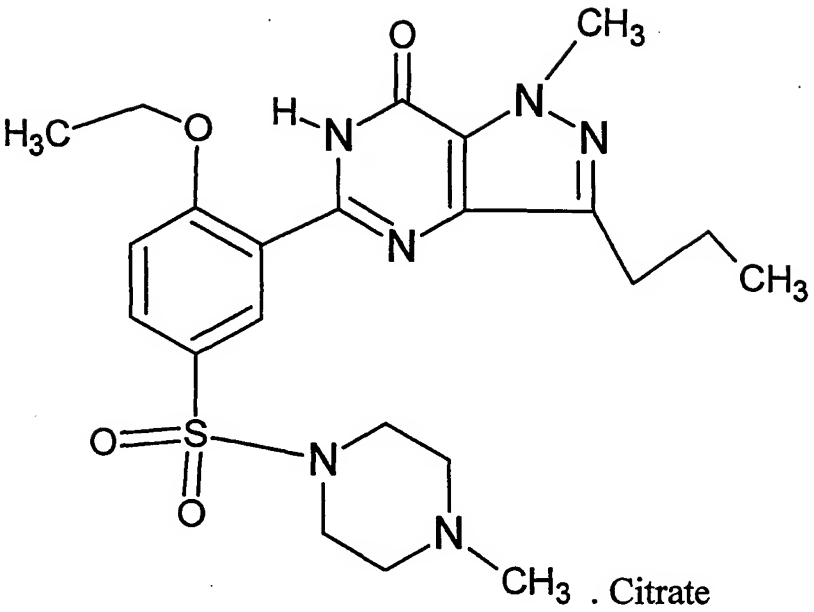


FIG. 3

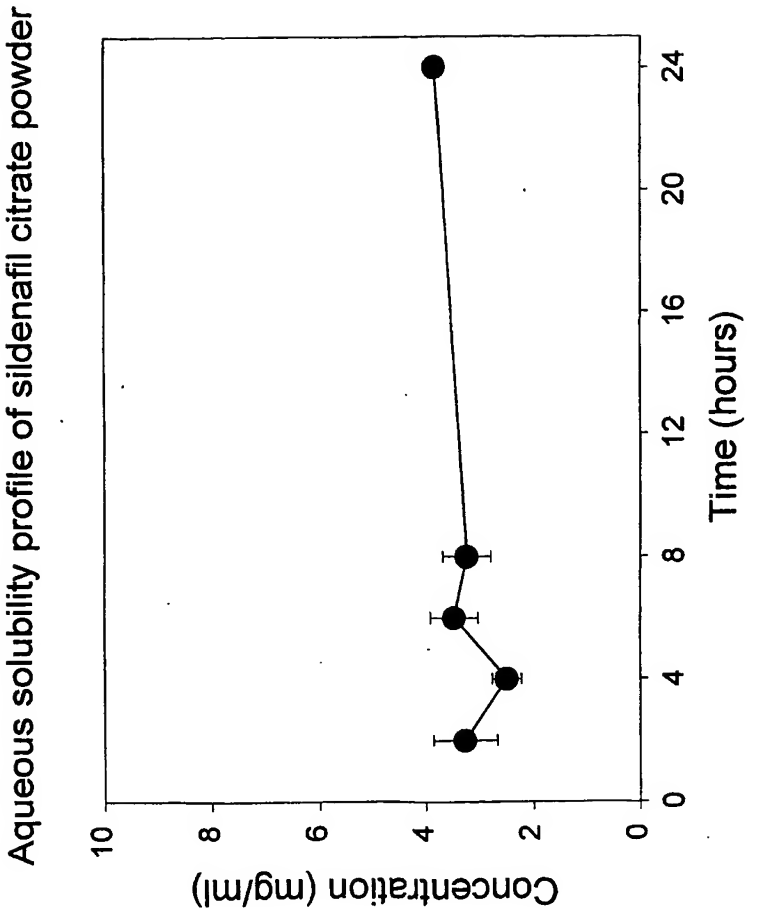

Aqueous solubility profile of sildenafil citrate powder
Concentration (mg/ml)
0
2
4
6
8
10
0
4
8
12
16
20
24
Time (hours)

FIG. 4

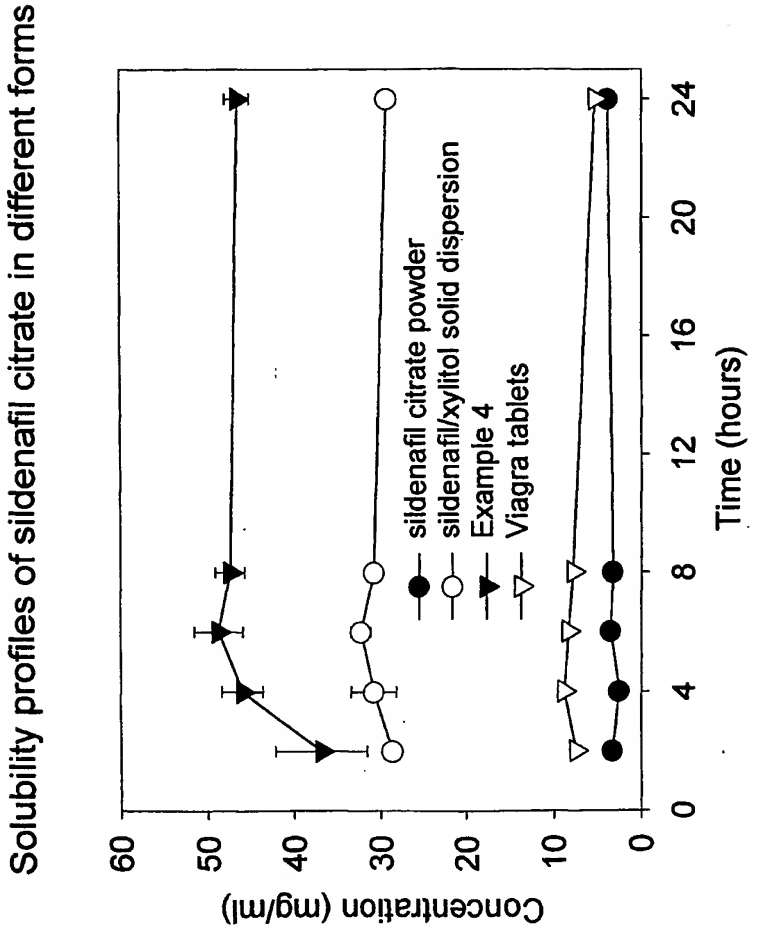

Solubility profiles of sildenafil citrate in different forms
Concentration (mg/ml)
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (hours)
sildenafil citrate powder
sildenafil/xylitol solid dispersion
Example 4
Viagra tablets

FIG. 5

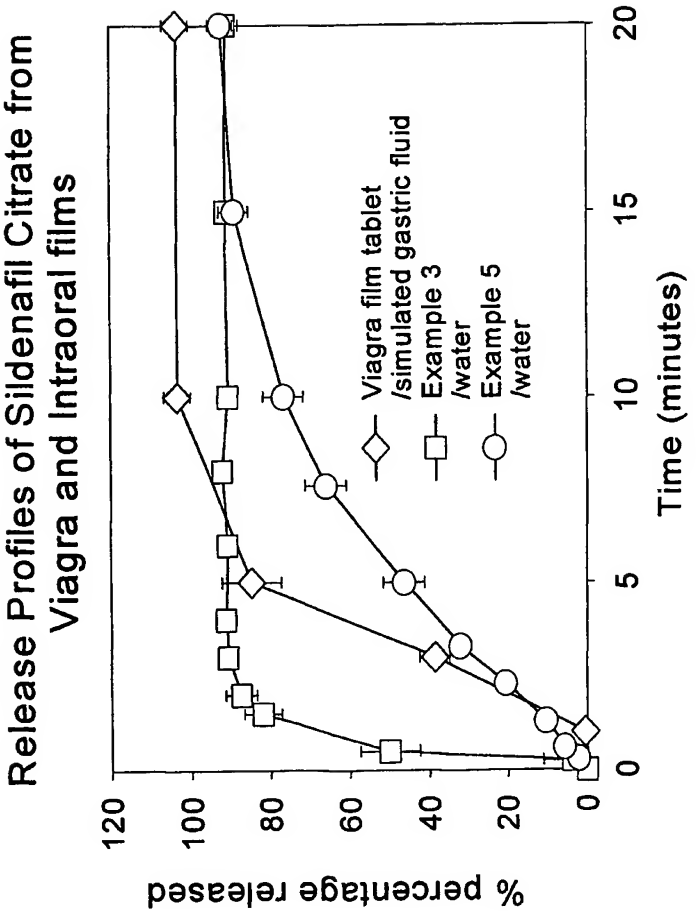

Release Profiles of Sildenafil Citrate from Viagra and Intraoral films
% percentage released
120
100
80
60
40
20
0
0
5
10
15
20
Time (minutes)
Viagra film tablet /simulated gastric fluid
Example 3 /water
Example 5 /water

FIG. 6

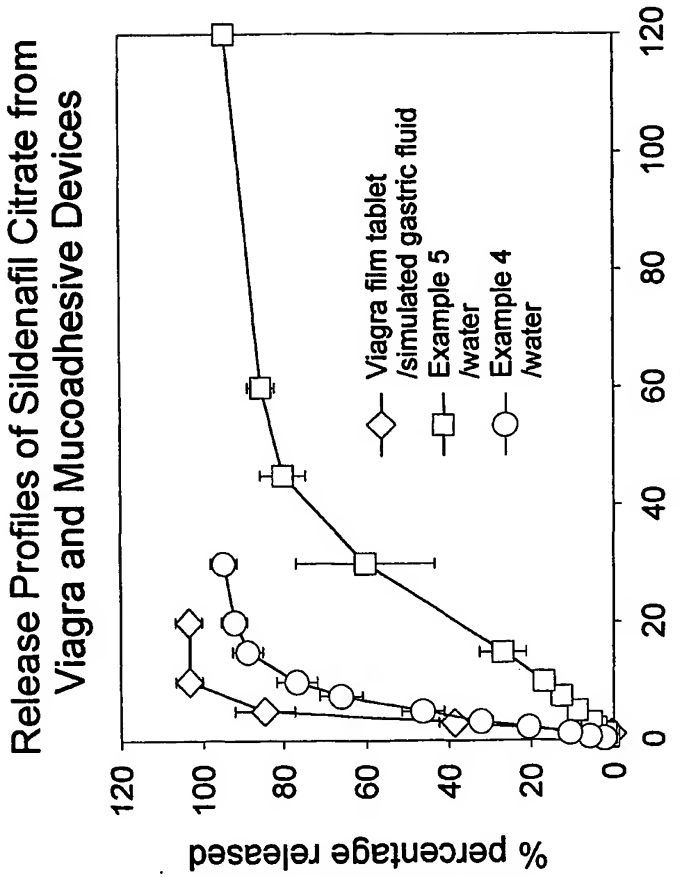

Release Profiles of Sildenafil Citrate from Viagra and Mucoadhesive Devices
% percentage released
120
100
80
60
40
20
0
0
20
40
60
80
100
120
Time (minutes)
Viagra film tablet /simulated gastric fluid
Example 5 /water
Example 4 /water

FIG. 7

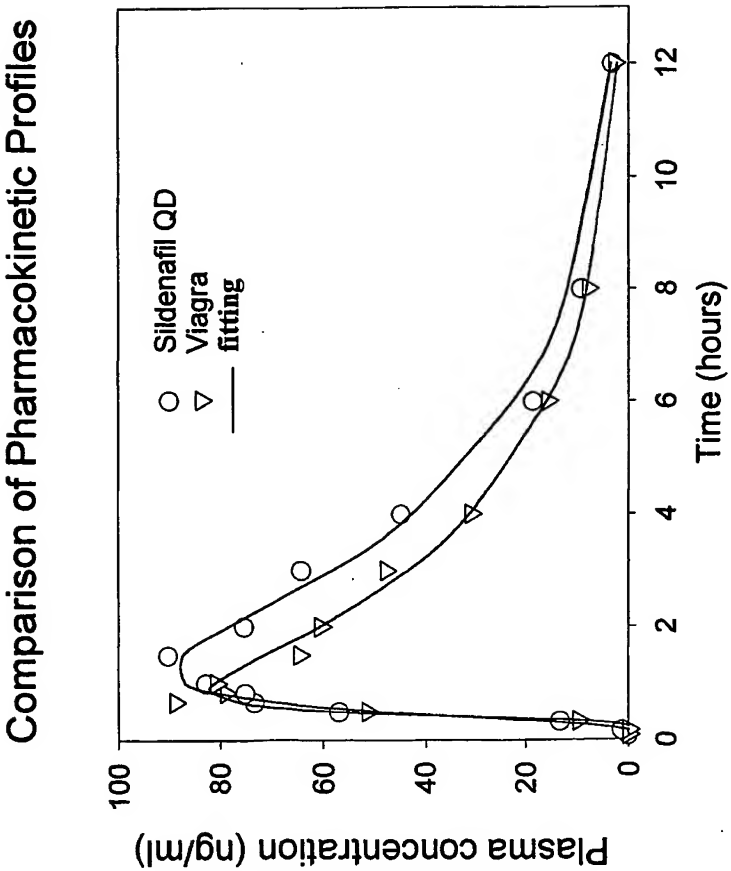

Comparison of Pharmacokinetic Profiles
Sildenafil QD
Viagra
fitting
Plasma concentration (ng/ml)
Time (hours)
0
20
40
60
80
100
0
2
4
6
8
10
12

FIG. 8

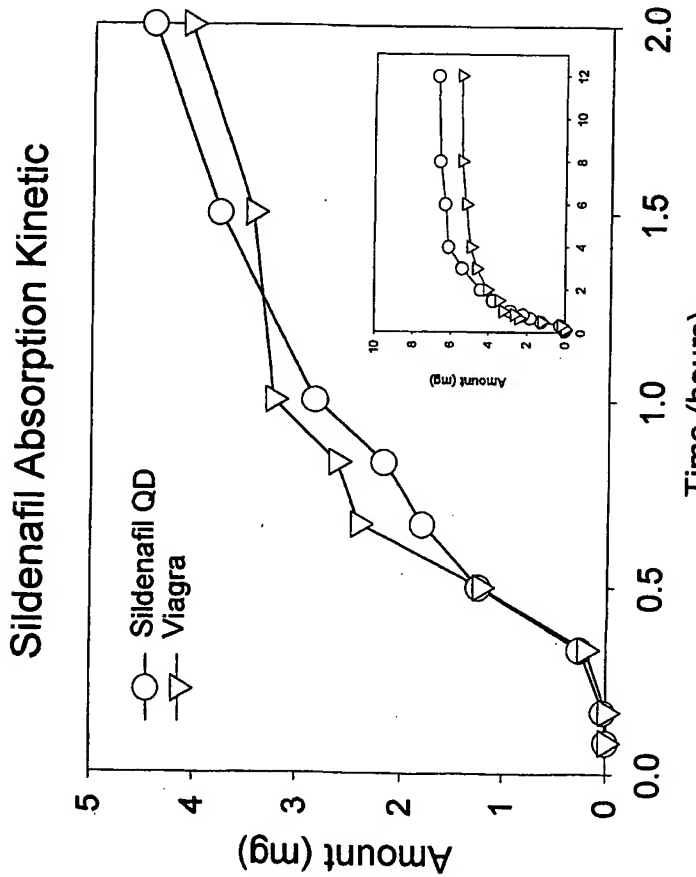
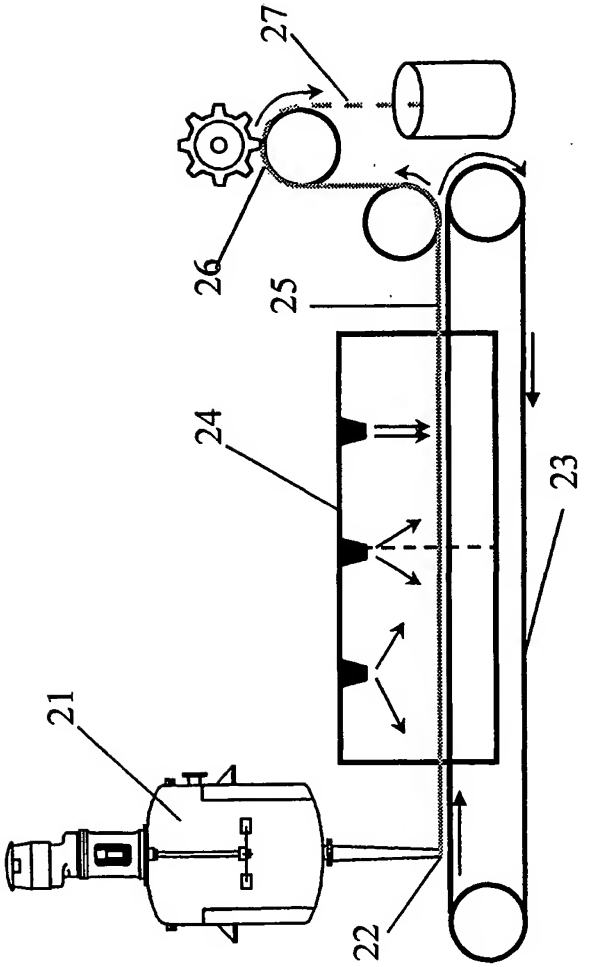
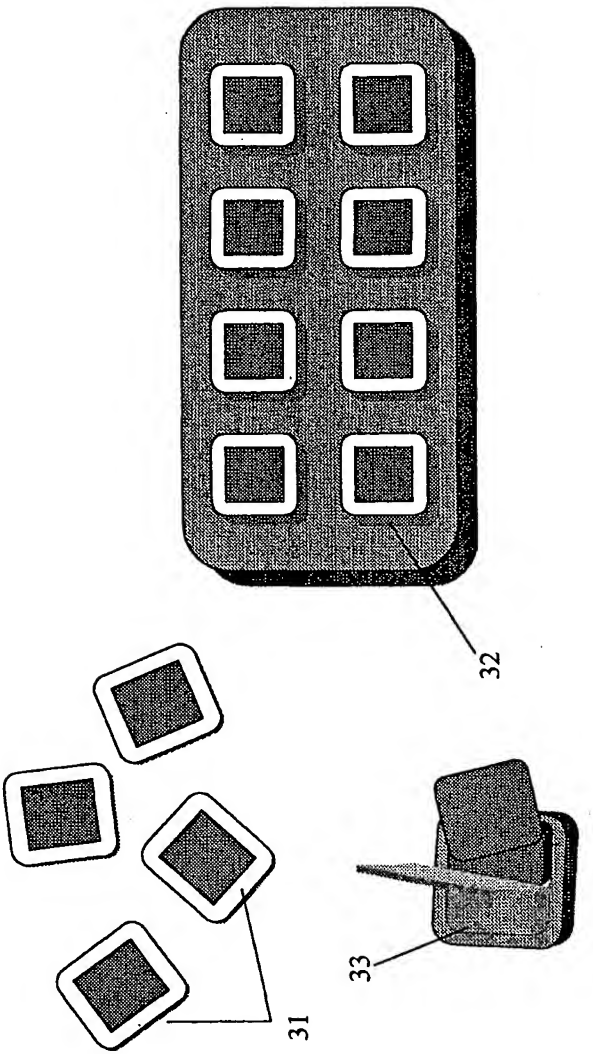

Sildenafil Absorption Kinetic
Sildenafil QD
Viagra
Amount (mg)
Time (hours)
0
1
2
3
4
5
0.0
0.5
1.0
1.5
2.0
Amount (mg)
0
2
4
6
8
10
12

FIG. 9



21 - mixing and degassing tank
22 - coating slot with thickness controller
23 - polyester backing belt
24 - drying oven with aeration controller
25 - quick dissolving intraoral film
26 - die cutting
27 - quick dissolving intraoral unit dose

FIG. 10



31 - single pouch 32 - multi-uints blister card
33 - multi-units dispensing pack

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/22538

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/495,31/505
US CL : 514/252.16,258
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/252.16,258

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	File DRUGLAUNCH, STN online, Acc. No. 1998:6847, Doc. No. 0168936, Drug Launches (May 18 1998), Abstract.	1
X	EP 0992240 A1 (MOCHIDA PHARMACEUTICAL CO.,LTD.) 12 April, 2000 (12.04.2000), page 4, lines 6-25, page 8, line 51, page 73, lines 37-46, page 80, lines 12-58, page 81, lines 1-25, pages 116-122, page 123, lines 1-10.	1-27, 37-43
X	File CAPLUS, STN online, Acc. No. 1998:724147, Doc. No. 130:43379, (JP 10298062 A2 (PFIZER PHARMACEUTICAL CO., LTD.) 10 November 1998 (10.11.1998)), Abstract.	1-4, 12-19, 24, 25-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"E" earlier application or patent published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 September 2001 (07.09.2001)	26 OCT 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Frank Choi Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/22538

Continuation of B. FIELDS SEARCHED Item 3:
STN/CAS,WEST

Search terms: sindenafil citrate, mannitol,xylitol,sorbitol,sucrose,dextrose,galactose,lactose,fructose,maltose